

REMARKS

Claims 54, 55, 57-60, 62, 63, 66 and 68-87 were pending in the application. Claims 54, 59, 68-71, 73-77, 79-84, 86, and 87 have been amended. Claims 55, 62, 63, 78 and 85 have been canceled. New claims 88-90 have been added. Claims 79, 80, 86, and 87 have been amended to change the dependency of the claim. Support for the amendment to claims 54, 59, 68-71, 73-77, and 81-84, as well as new claims 88-90, can be found in the claims as originally filed and throughout the specification. Following entry of this Amendment and Response, claims 54, 57-60, 66, 68-77, 79-84, and 86-90 will be pending.

The specification has been amended to correct typographical errors.

No new matter has been added. The foregoing claim amendments and cancellations should in no way be construed as an acquiescence to any of the Examiner's rejections, and have been made solely to expedite the prosecution of the application. Applicant reserves the right to pursue the claims as originally filed in this or a separate application(s).

Specification amendments

At the request of the Examiner, the specification has been amended to correct for typographical errors relating to Example 9.

Claim objections

The Examiner has objected to claims 55, 60, 62, and 63 as containing non-elected subject matter because the claims encompass non-elected species. It is Applicant's understanding that the species election was for searching purposes only, as the cited claims depend from generic linking claim 54. It is Applicant's understanding that upon allowance of the elected species, the remaining species also will be searched (37 C.F.R. § 1.141).

Rejection of Claims 59, 63, and 73 under 35 U.S.C. § 112, Second Paragraph***I. Rejection of Claim 59 under 35 U.S.C. § 112, Second Paragraph***

The Examiner has rejected claim 59 under 35 U.S.C. § 112, second paragraph for use of the phrase "the LT- β -R blocking agent comprises a soluble LT- β -R further comprising a human immunoglobulin Fc domain." The Examiner asserts that "[i]t is unclear because of the sentence syntax whether the blocking agent or the soluble LT- β -R further comprises a human IgG Fc

domain.” In order to expedite prosecution of the application, Applicant has amended claim 59 to specify a soluble LT- β -R fused to one or more heterologous protein domains. Applicant has also added new claim 88 which depends from claim 59, and specifies that the heterologous protein domain comprises a human immunoglobulin Fc domain. In view of the amendment to claim 59 and the addition of new claim 88, Applicant respectfully requests that the 35 USC 112, second paragraph rejection be withdrawn.

II. Rejection of Claim 63 under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claim 63 under 35 U.S.C. § 112, second paragraph. The Examiner asserts that the term “subunit” is indefinite “because it is unclear which subunit is encompassed” by the term.

Applicant respectfully traverses the foregoing rejection on the grounds that claim 63 particularly points out and distinctly claims the subject matter which Applicant regards as the invention as required by 35 U.S.C. § 112, second paragraph. Based on the plain language of the claim and the teachings in Applicant’s specification, the term “subunit” is clear and definite to one of ordinary skill in the art who would recognize that the term “subunit” includes either of the molecular subunits, *i.e.*, LT- α or LT- β , or the combined complex, which make up the LT- β -R ligand. In order to expedite prosecution of the application, however, claim 63 has been cancelled, thus rendering the rejection moot.

III. Rejection of Claim 73 under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claim 73 under 35 U.S.C. § 112, second paragraph for use of the phrase “functional sequence of amino acids.” The Examiner asserts that the term “functional sequence” is unclear.

Applicant respectfully traverses the foregoing rejection on the grounds that claim 73 particularly points out and distinctly claims the subject matter which Applicant regards as its invention, as required by 35 U.S.C. § 112, second paragraph. Claim 73 has been amended to require that the functional sequence comprise the LT- β -R ligand binding domain. In addition, Applicant submits that one of ordinary skill in the art would recognize that a soluble LT- β -R comprising a functional sequence of amino acids from the amino acids of SEQ ID NO: 1 includes any sequence from SEQ ID NO: 1 which encodes a protein having LT- β -R biological

activity. The term “LT- β -R biological activity” is defined at page 10, lines 35-38 of the specification as referring to “1) the ability of the LT- β -R molecule or derivative to compete for soluble or surface LT ligand binding with soluble or surface LT- β -R molecules ; or 2) the ability to stimulate an immune regulatory response or cytotoxic activity in common with a native LT- β -R molecule.” Therefore, one of ordinary skill in the art would know from the clear definition provided in the specification that any soluble LT- β -R comprising a functional sequence would include any sequence which could compete for binding for the LT ligand with a surface or soluble LT- β -R or stimulate a signaling response like that of native LT- β -R. Based on the plain language of the amended claim and the teachings in Applicant’s specification, claim 73 is clear and definite to one of ordinary skill in the art who would understand soluble LT- β -R molecules which comprise a “functional sequence.” Accordingly, Applicant respectfully requests that the rejection of claim 73 under section 112, second paragraph be reconsidered and withdrawn.

Rejection of Claims under 35 U.S.C. § 112, First Paragraph

I. Rejection of Claims 54, 55, 57, 58, 66, 68-87 under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claims 54, 55, 57, 58, 66, 68-87 under 35 U.S.C. § 112, first paragraph. The Examiner asserts that the specification does not enable one of ordinary skill in the art to perform the invention, stating that while the application is enabled for methods relating to the inhibition of LT- β -R signaling for treating a human subject suffering from any autoimmune disorder or any chronic inflammatory disorder where the LT- β -R blocking agent is soluble LT- β -R or an LT- β -R IgG fusion protein, the specification does not enable the method of the invention for any LT- β -R blocking agent. Applicant respectfully traverses this rejection.

The claims have been amended to specify a method for inhibiting lymphotoxin- β -receptor (LT- β -R) signaling in a subject having an autoimmune disorder or a chronic inflammatory disease comprising administering to the subject a pharmaceutical composition comprising an effective amount of an LT- β -R blocking agent, and a pharmaceutically acceptable carrier, wherein the LT- β -R blocking agent comprises a soluble LT- β -R or an antibody directed against LT- β -R. As evidenced in Applicants’ specification, the presently claimed methods are fully enabled such that one of ordinary skill in the art could practice the claimed invention without undue experimentation.

The Examiner asserts that undue experimentation is required as the claims are drawn to a range of LT- β -R blocking agents which are not supported by the specification. The Examiner also alleges that the specification does not adequately describe how to make and use LT- β -R blocking agents. In contrast to the Examiner's position, Applicant submits that one of ordinary skill in the art could make and use the LT- β -R blocking agents used in the methods of the invention based on the teachings in the specification and the common knowledge in the art at the time of filing.

The specification discloses a number of examples of LT- β -R blocking agents, including soluble LT- β -R-Fc molecules and antibodies, such as anti-LT- α , anti-LT- β , anti-LT- α/β , and anti-LT- β -R antibodies (see page 10, lines 21-34), as well as methods for making said LT- β -R blocking agents. For example, Applicant teaches how to make soluble LT- β -R molecules, including which portions of LT- β -R should be included in the soluble LT- β -R, *i.e.*, any functional portion of the extracellular domain including the ligand binding domain (see pages 19-23 of specification). Applicant also provides working examples detailing how to make a human and murine LT- β -R Fc fusion protein (see Examples 1 and 2). The specification also teaches examples of heterologous proteins which may be fused to the soluble LT- β -R. Applicant further provides working examples of a soluble LT- β -R which can be used as an LT- β -R blocking agent, including *in vivo* experiments using LT- β -R-Ig fusions to effectively inhibit LT- β -R signaling in murine models for contact hypersensitivity (Example 8), inflammatory bowel disease (IBD) (Example 9), and delayed type hypersensitivity (Example 11).

In another example, Applicant teaches that antibodies which inhibit LT- β -R from binding surface LT ligand may be used as LT- β -R blocking agents of the invention, such as anti-LT- β -R antibodies. Applicant teaches how to make and identify such antibodies which may be used as LT- β -R blocking agents at page 24-32 of the specification. Applicant also provides examples of anti-LT- β -R antibodies, including antibody BDA8. Example 5 of the specification describes *in vitro* experiments which show that anti-LT- β -R antibody BDA8 can act as an LT- β -R blocking agent as it is able to restore the ability of tumor cells to grow in the presence of an LT- β -R activating agent. Furthermore, Example 7 describes use of the anti-LT- β antibody B9 (LT- β being one of the subunits which make up the LT ligand) to block binding of LT- β -R to its ligand. Accordingly, one of ordinary skill in the art is provided ample guidance with respect to how to

make and use LT- β -R blocking agents, as multiple examples, including working examples, are described in the specification.

In contrast to the Examiner's assertion, ample guidance regarding how to make and use therapeutically effective LT- β -R blocking agents is provided by the instant specification and by the knowledge in the art at the time of priority. As acknowledged by the Examiner, the specification describes several studies demonstrating *in vivo* use of an LT- β -R blocking agent in a murine disease model, including IBD and DTH. At page 29, lines 1-3, Applicant teaches that Th1-cell mediated disorders, including DTH, can be treated using LT- β -R blocking agents. The specification describes at page 33, lines 29-35, that many organ-specific autoimmune conditions, such as multiple sclerosis and psoriasis, are associated with a Th1 response, and, therefore, could be treated using LT- β -R blocking agents. The specification provides literature references which describe data supporting the connection between Th1 responses and autoimmune conditions. At page 34, lines 1-13, the specification also teaches that LT- β -R blocking agents may be used to treat the autoimmune disease diabetes. Applicant teaches examples of other Th1-cell mediated disorders, including autoimmune conditions and chronic inflammatory diseases, at page 14, lines 19-34 which may be treated using the method of the invention. Accordingly, overall, Applicants' specification provides a considerable amount of guidance as to how to practice the claimed methods such that one of ordinary skill would not have to perform undue experimentation.

The Examiner asserts that Applicant has failed to prove the therapeutic efficacy of the claimed invention because Applicant has not provided working examples for other types of autoimmune conditions and chronic inflammatory diseases. ***Applicant submits that the data presented in the Examples section of the specification supports the therapeutic methods of the invention, and should not be used to limit the scope of the claimed invention.*** The LT- β -R blocking agents described in the working examples are representative of the claimed LT- β -R blocking agents described in the specification. Furthermore, the murine models taught in the specification are representative of autoimmune disorders and chronic inflammatory diseases in general and should not be used to limit the claimed invention as suggested by the Examiner. In order to meet the enablement requirement, it is not necessary that a patent specification include specific examples of every different embodiment encompassed by the claims. Furthermore, the enablement requirement is satisfied if the specification contains sufficient information regarding

the subject matter of the claims to enable one of ordinary skill in the art to make and use the claimed invention without undue experimentation (MPEP 2164).

In sum, Applicant has provided sufficient guidance with respect to examples of LT- β -R blocking agents, including examples of said blocking agents and methods for how to make and identify additional agents. Applicant has also provided working examples using different types LT- β -R blocking agents, including soluble LT- β -R IgG fusion proteins and anti-LT- β -R antibodies, to inhibit LT- β -R and treat various disorders using *in vivo* animal models. Applicant submits that the Examiner has failed to provide any evidence in support of her position that one of ordinary skill in the art would not reasonably extrapolate from successful experiments showing LT- β -R inhibition using the *in vivo* models described by Applicants.

Finally, the Examiner states that treatment of autoimmune disorders and chronic inflammatory diseases is unpredictable, and, therefore, would require undue experimentation. In support of this position, the Examiner cites Browning *et al.* (1993) *Cell* 72:847 as teaching unpredictability in the art. First, Applicant notes that the Browning reference is not reflective of the state of the art at the time of filing, as it was published more than two years prior to Applicant's priority date. The Browning reference was published at a time when the identification of LT- β -R had not yet occurred, and describes the identification of LT- β , which is one of the subunits which comprise the LT- β -R ligand (surface LT ligand). The Examiner cites Browning as teaching that the TNF and LT pathways are " 'somewhat of an enigma' " as *in vitro* and *in vivo* data have not coincided and painted a clear picture of the involvement of these pathways in T and B cell regulation. Applicant respectfully points out that the invention is directed to the inhibition of LT- β -R signaling, thus making experiments relating to TNF irrelevant. Moreover, the working examples provided by Applicant stand in contrast to the comments in Browning cited by the Examiner, as Applicant provides working examples which show that LT- β -R blocking agents work effectively both *in vitro* and *in vivo* to inhibit LT- β -R signaling. Applicant further shows that such inhibition can be used to treat autoimmune disorders and chronic inflammatory diseases using animal disease models. There is no teaching or suggestion in Browning that inhibition of LT- β -R signaling comprising administration of an LT- β -R blocking agent to a subject having autoimmune disorder or a chronic inflammatory disease is unpredictable. As such, the Browning reference cited by the Examiner does not establish unpredictability in the field at the time of filing, as the reference was published prior to

the identification of LT- β -R and does not relate to LT- β -R inhibition as required by the methods of the claims.

In view of the above, Applicant submits that the specification fully enables one of ordinary skill in the art to make and use the claimed invention, and respectfully request that the Examiner withdraw the 112, first paragraph rejection regarding enablement of the claims.

II. Rejection of Claims 54, 55, 57-60, 62, 63, 66, and 68-72 under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claims 54, 55, 57-60, 62, 63, 66, and 68-72 under 35 U.S.C. § 112, first paragraph for failing to comply with the written description requirement. The Examiner asserts that the claimed invention “encompasses numerous species that are not further described.” Applicant respectfully traverses this rejection.

As described by the Examiner, in order to satisfy the written description requirement for a claim drawn to a genus, the claimed genus may be described through a representative number of species by disclosure of relevant identifying characteristics of the genus. The Examiner claims that a number of genera are encompassed by the claims but are not supported under the written description requirement. The Examiner claims that the specification lacks support for soluble LT- β -R, antibodies directed against LT- β -R, antibodies directed against surface LT ligand, and surface LT ligands. Applicant submits that the specification satisfies the written description requirement by providing a representative number of species for each of the genera cited by the Examiner as lacking written description support. In the interest of facilitating prosecution, Applicant notes that claims 55, 62, and 63 have been cancelled and claim 54 has been amended to specify LT- β -R blocking agents comprising a soluble LT- β -R or an anti-LT- β -R antibody.

The Examiner suggests that the specification lacks written support for the genus of soluble LT- β -R. Applicant submits that the specification provides examples of soluble LT- β -R molecules, as well as how to make and identify other versions of soluble LT- β -R which could act as an LT- β -R blocking agent in accordance with the claimed methods. Applicant provides working examples of a soluble LT- β -R molecule, including a human and mouse LT- β -R IgG fusion protein in Examples 1 and 2, respectively. Applicant also teaches that alternative versions of soluble LT- β -R may be constructed using the sequence of the extracellular portion of LT- β -R

provided in Figure 1 (SEQ ID NO: 1) and recombinant DNA techniques known in the art (see specification at page 19, line 25 to page 22, line 27). Applicant teaches that functional fragments encoding the ligand binding domain of LT- β -R may be used to in soluble LT- β -R molecules, wherein all or a portion of the LT- β -R extracellular regions as described in SEQ ID NO: 1 comprising the LT- β -R ligand binding domain may be fused to an heterologous protein, such as an immunoglobulin constant region like an Fc domain (see page 20, lines 15-23). Applicant further provides a reference, US 5,225,538, which provides methods for the construction of receptor-Ig proteins. Applicant notes that the cited reference is incorporated by reference. As such, Applicant provides a working example of a soluble LT- β -R described in the claims, as well as methods of making additional soluble LT- β -R constructs. Applicant teaches that soluble LT- β -R may be fused to other types of heterologous proteins (other than Fc domain), including serum albumin, lipoproteins, apolipoproteins, and transferring (see page 20, lines 1-14). Furthermore, it should be noted that in the recent *Capon v. Eshhar* decision regarding a chimeric gene, the Court held that it is not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize a generic invention. See *Capon v. Eshhar v. Dudas* (Fed. Cir. 2005). Thus, one of ordinary skill in the art would recognize based on knowledge in the art at the time of filing and Applicant's teachings in the specification, that a soluble LT- β -R would include any amino acid sequence from SEQ ID NO: 1 which contained a functional LT- β -R ligand binding domain.

With respect to the genus of anti-LT- β -R antibodies, the specification teaches that an antibody directed against LT- β -R includes "any antibody that specifically binds to at least one epitope of the LT- β receptor" (see page 10, lines 13-15). The specification provides an example of such an anti-LT- β -R antibody, *i.e.*, BDA8 (see page 17, lines 18-19). In addition to providing a working example, Applicant teaches how to make and identify other anti-LT- β -R antibodies which could be used as LT- β -R blocking agents in the methods of the invention (see screening methods describe at page 17, line 14 to page 19, line 23 and page 26, lines 4-22, as well as sources of anti-LT- β -R antibodies described at page 24, line 1 to page 26, lines 3 of specification). As described in M.P.E.P. section 2163 II.A.3.a.ii., a sufficient "representative number" of species of the claimed genus is "an inverse function of the skill and knowledge in the art." Applicant submits that based on teachings in the specification and the knowledge in the

art at the time of filing, one of ordinary skill in the art would be able to predict other species of anti-LT- β -R antibodies.

Generally, the specification teaches that LT- β -R blocking agents all have the common characteristic of being capable of diminishing ligand binding to LT- β -R, cell surface LT- β -R clustering or LT- β -R signaling, and also provides representative species of the claimed genus and subgenus which share this common functional characteristic. Applicant provides screening methods for identifying additional types of LT- β -R blocking agents at pages 17-19 of the specification. For example, Applicant teaches that an agent that can inhibit the cytotoxic effect of an LT- β -R activating agent on a tumor cell is an agent which can inhibit LT- β -R signaling, *i.e.*, an LT- β -R blocking agent. Based on teachings in the specification and the knowledge in the art at the time of filing, one of ordinary skill in the art would be able to predict other species of LT- β -R blocking agents other than those disclosed in the various subgenera described by the Examiner. Furthermore, as described in the M.P.E.P. section 2163 II.A.3.a.ii., a sufficient “representative number” of species of the claimed genus is “an inverse function of the skill and knowledge in the art.” Based on the teachings of the specification, one of ordinary skill in the art could predict additional LT- β -R blocking agents, including additional species of soluble LT- β -R and antibodies directed against LT- β -R, by determining whether such an agent inhibits LT- β -R signaling, such as the ability of the agent to block LT ligand-mediated anti-proliferative effects on cells *in vitro*, using common methods known in the art.

In sum, the written description requirement under U.S.C. 112, first paragraph is satisfied for the representative species of the genera cited by the Examiner, *i.e.*, soluble LT- β -R, antibodies directed against LT- β -R, as the instant specification describes a representative number of species for each genera with a common, identifying characteristic, *i.e.*, ability to inhibit LT- β -R signaling. As such, one of ordinary skill in the art would recognize that Applicant was in possession of the claimed invention at the time of filing, thus satisfying the requirement for written description. Therefore, Applicant respectfully requests that the Examiner withdraw the 35 U.S.C. § 112, first paragraph rejection of claims 54, 55, 57-60, 62, 63, 66, and 68-72.

Rejection of Claims 54, 55, 57-59, 66, 68-74, 76, 77, 78, 81, and 83-85 Under 35 U.S.C. §103(a) over Crowe *et al.* in view of Mohler *et al.*

The Examiner has rejected claims 54, 55, 57-59, 66, 68-74, 76, 77, 78, 81, and 83-85 as being obvious in view of Crowe *et al.* (1994) *Science* 264:707 (hereinafter Crowe) in combination with Mohler *et al.* (1993) *J. Immunol.* 151:1548 (hereinafter Mohler). Applicant respectfully traverses this rejection.

The Examiner states that Crowe teaches the sequence of LT- β -R, but does not teach “administration of a soluble LT- β -R fused to IgG for inhibiting the lymphotoxin-beta-receptor.” In view of this deficiency, the Examiner cites Mohler as teaching Fc fusion proteins comprising TNF receptors and administration of such recombinant soluble receptors for inhibiting inflammatory and immune responses. The Examiner suggests that it would have been obvious for one of ordinary skill in the art “to have made a fusion protein comprising the soluble LT- β -R (SEQ ID NO: 1) taught by Crowe, *et al.* and fused to a human immunoglobulin Fc domain as taught by Mohler, *et al.*” The Examiner also suggests that one of ordinary skill in the art would have been motivated to “construct the fusion protein because Mohler *et al.* teach that fusion proteins are more potent as competitive inhibitors than monomeric soluble receptors.”

A proper *prima facie* obviousness rejection requires that the prior art reference (or references when combined) must teach or suggest all the claim limitations. See M.P.E.P. § 2143. Also, see *In re Vaack*, 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1443 (Fed. Cir. 1991) (the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure). In addition, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Finally, there must be a reasonable expectation of success. Applicant submits that the Examiner has failed to establish a *prima facie* case of obviousness because none of the three required elements are met in accordance with a proper obviousness rejection.

As acknowledged by the Examiner, Crowe does not teach administration of soluble LT- β -R fused to an IgG to a subject for inhibiting LT- β -R. Applicant notes that Crowe also does not teach a pharmaceutically acceptable carrier, as required by the amended claims. Thus, Crowe provides no suggestion of the limitations of the pending claims.

The secondary reference cited by the Examiner, *i.e.*, Mohler, does not account for the deficiencies of Crowe. Mohler describes a comparative study of monomeric and dimeric (Fc fusion proteins) TNFR (also referred to as the p80 cell-surface receptor for TNF) and the ability of the monomeric and dimeric construct to inhibit TNF activity in a murine sepsis model. Applicant submits that Mohler does not teach or suggest administration of a composition comprising, to a subject having for inhibition of LT- β -R signaling, as required by the pending claims. While LT- β -R and TNFR are both members of the same family of TNF receptors, the Examiner has failed to indicate why Mohler accounts for the deficiency of Crowe by teaching administration of a different receptor, *i.e.*, TNFR, for the inhibition of TNFR signaling for treating sepsis. Furthermore, Mohler does not teach a pharmaceutical composition comprising an LT- β -R blocking agent, such as a soluble LT- β -R, and a pharmaceutically acceptable carrier, as required by the amended claims. Finally, Mohler does not teach administration of an LT- β -R blocking agent, such as a soluble LT- β -R, to a subject having an autoimmune disorder or a chronic inflammatory disease, as required by the amended claims. Thus, neither Mohler nor Crowe teaches all of the required elements of the claims either alone or in combination.

In addition, there is no suggestion or motivation for one of ordinary skill in the art to combine the teachings of Mohler and Crowe. The Examiner suggests that one of ordinary skill in the art would have been motivated to construct an LT- β -R Fc fusion protein based on the teachings of Mohler, and furthermore, that one of ordinary skill in the art would have been motivated to “administer the soluble LT- β -R complex for treatment in chronic inflammatory and autoimmune diseases because LT- β -R as part of the TNF family plays a role in inflammatory and immune responses.” Applicant respectfully disagrees. Crowe teaches that LT- β -R is unique in comparison to other TNF receptors, such as those taught by Mohler. At page 708, second column, Crowe notes that while certain portions of the extracellular structure of LT- β -R have similarity to a number of TNF receptors, the “cytoplasmic region of LT- β -R has little sequence similarity with other members of the receptor family, which suggests that the mechanism used to signal cellular responses may diverge from TNFR” (see page 708, second column, first paragraph). Crowe teaches that molecular distinctions between TNFR and LT- β -R may likely result in distinct signaling pathways. Thus, there is no motivation for one of ordinary skill in the art to combine the teachings of Mohler with Crowe.

The last element to establishing a *prima facie* case of obviousness is that there must be a reasonable expectation of success. The results described by Mohler are somewhat ambiguous in that Fc TNFR fusion protein acts as both an agonist and an antagonist to serum TNF in a “dose-dependent fashion” using the sepsis murine model (see conclusion, page 1559, first column). One of ordinary skill in the art would not have a reasonable expectation of success to arrive at the claimed method of inhibition based on the experiments described in Mohler, as the cited reference teaches that sTNFR:FC molecule is unpredictable in that it acts as both an inhibitor and an activator. Furthermore, as described above, Crowe teaches that LT- β -R is a unique member of the TNF receptor family, and, therefore, one of ordinary skill in the art would not have an expectation of success in applying the methods specific to TNFR as taught by Mohler to inhibit LT- β -R signaling in a subject.

In view of the foregoing, Applicant submits that the Examiner has failed to support a *prima facie* case of obviousness. Neither of the two cited references teaches all of the elements of the claimed invention, as Mohler does not cure the deficiencies of Crowe. Moreover, the Examiner has not provided explicit support from the cited references which would lead one of ordinary skill in the art to be motivated to combine the two references or have an expectation of success at arriving at the claimed invention. Thus, Applicants respectfully request that this rejection be withdrawn.

Information Disclosure Statement

Applicant respectfully notes that to date Applicant has not received an indication that the Examiner has considered the references described in the Information Disclosure Statement filed with the application on February 15, 2002. Applicant respectfully requests that the Examiner provide an initialed copy of PTO-Form 1449 which was filed on February 15, 2002 to indicate that said references have been considered.

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The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 12-0080, under Order No. BGNB191CPUSDV.

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Respectfully submitted,

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